Phorphyrins, Calixpyrroles and Cucurbituril like Macrocycles containing Pyrrolidone Functionality

By: Robert B. Login

Abstract:

A great deal of interest has been and continues to revolve around these three classes of macrocycles; however, I have not found references to any that were derivatised with pyrrolidone functionality(?). Such derivatives would be expected to afford unique properties such as superior complexation and water solubility. Such pyrrolidone functionalized derivatives might very well compete with PVP complexes because of a better safety profile. In addition, unique applications maybe revealed such as safe easily excreted synthetic blood components, or drug delivery systems. The relative simplicity of the chemistry is also very attractive. Acceptable yields of similar molecules suggests the potential success of pyrrolidone analogs; however, optimization of the reactions needed for successful commercialization would still be required. These macrocyclic structures present pyrrolidone with a superior complexation potential because of the close proximity of the pyrrolidone groups to the nitrogens of the pyrrole ring.

Prior Art:

Formation of pyrrole based macrocycles has been known since the late 1800's when Otto Bayer condensed pyrrole with acetone using HCl as the catalyst. Since then renewed interest occurred when the actual structure of these macrocycles based on the condensation of aldehydes and ketones with pyrrole was confirmed. The fact that the same four pyrroles could form the same ring structure as found in nature, and could be easily achieved with this simple chemistry aroused significant interest. Chlorophyl the

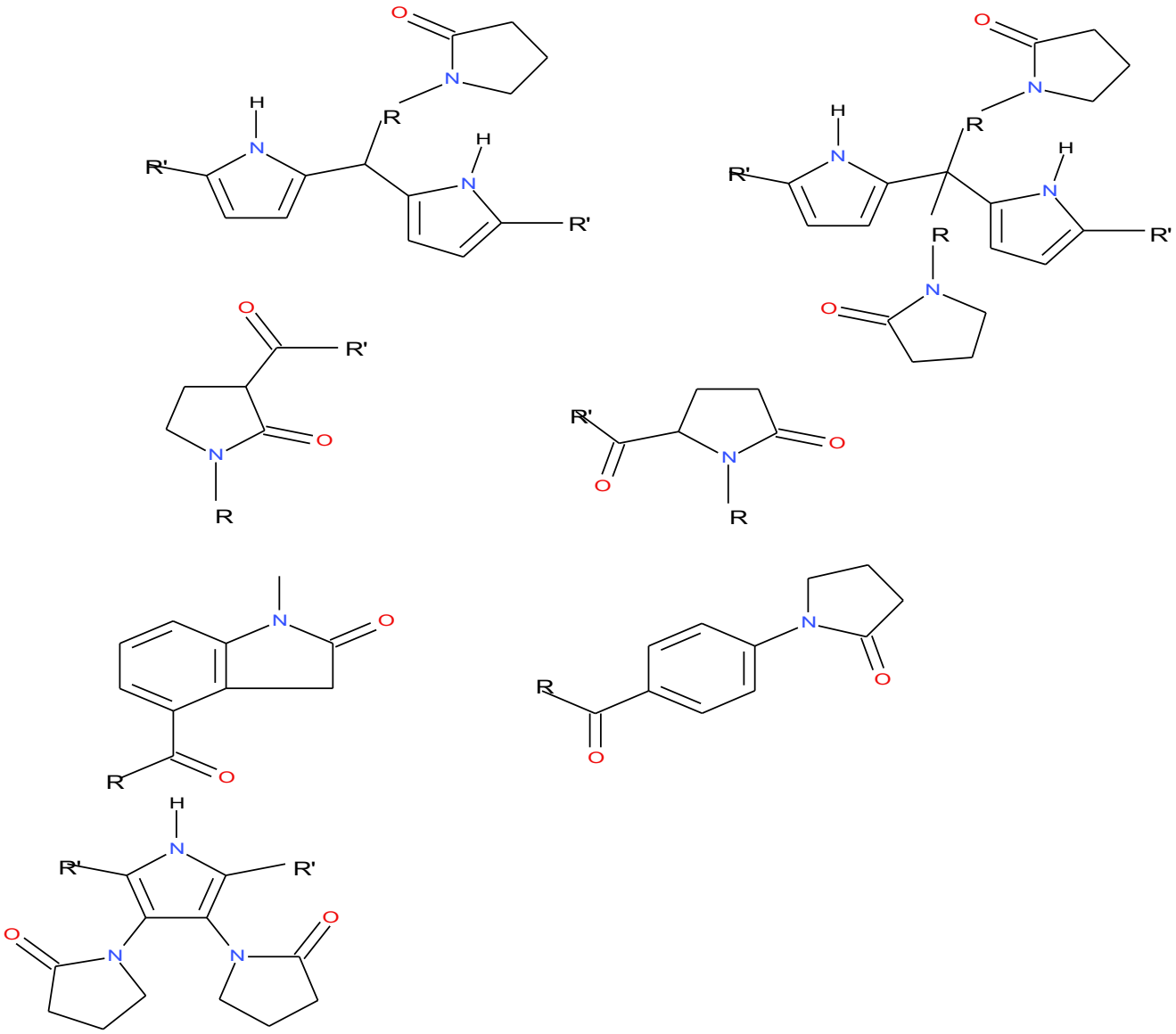
basis of all current life on this planet as well as Heme without which we would not exist, are based on cyclic condensation of four pyrroles. Nature has created this chemistry and the systems required to exploit their potential over eons of time, to perfect these molecular factories.

Porphyrins are aromatic 4N+2 18 electron condensates of pyrrole and formaldehyde catalyzed with acid to form initially a porphyrinogen intermediate that can be readily oxidized to the porphyrin. A variety of aldehydes can be employed to afford numerous meso(the bridging carbon between pyrroles) modified porphyrins. Additional modifications can be obtained by use of the beta position on the ring pyrroles. What would pyrrolidone meso derivatives contribute to porphyrin chemistry? First off solubility in both polar and non-polar solvents, ability to complex a variety of molecules such as ionic metals and cationic compounds, and potentially the ability to safely deliver complexed molecules to living target organs.

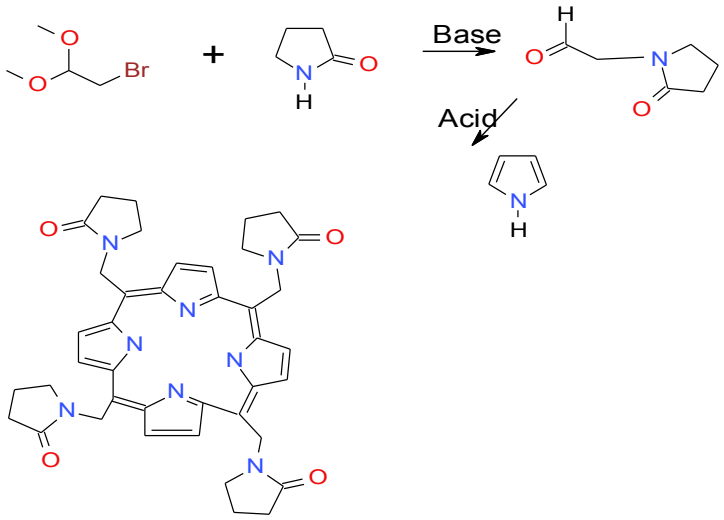
Pyrrolidone can be drawn in two resonance forms with a positive charge on nitrogen and a negative charge on oxygen. However, when in large structures like PVP for example, it can attract protons so that it is now positively charged. Such positively charged macrocycles can complex anionic molecules while the pyrrole ring is well known to complex cations like magnesium ions. Pyrrolidone is also associated with reduced toxicity. Porphyrins and their metal ion complexes are colored molecules whose color can be varied by the pyrrolidone location and structure of its associated functionalities and if its positively charged or neutral. These derivatives can be structured to act as catalysts, optical sensors, ion-selective electrodes, HPLC supports, to name a few. The same conclusions can be applied to the pyrrolidonecalixpyrrole structures. In this case the meso carbon is sp3 and cannot be oxidized to aromatic porhyrin type macrocycles. Both pyrrolidonecalixpyrrole and pyrrolidoneporhyrins can be visualized with a very large variety of structures depending on what else is on the pyrrole or pyrrolidone and what other heterocycles are part of the macrocycles. “Macrocycles, construction, chemistry and nanotechnology applications”, by Davis and Higston (Wiley, 2011) and

Quo vadis porphyrin chemistry by V. Kral et. al. Physiol Res. 55(Suppl. 2): S3-S26, 2006; have very detailed reviews of these macrocycles and their chemistry and should be reviewed for more detailed information.

Potential pyrrolidone containing porhyrin and calixpyrrole precursor Aldehydes and Ketones :

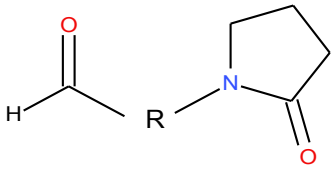


The R groups can be the same structure to afford symmetrical ketones or hydrogen. The above is not meant to be exhaustive but suggestive. I must point out that pyrrole can be synthesized from cis-butene-1,4-diol and other acetylenics.



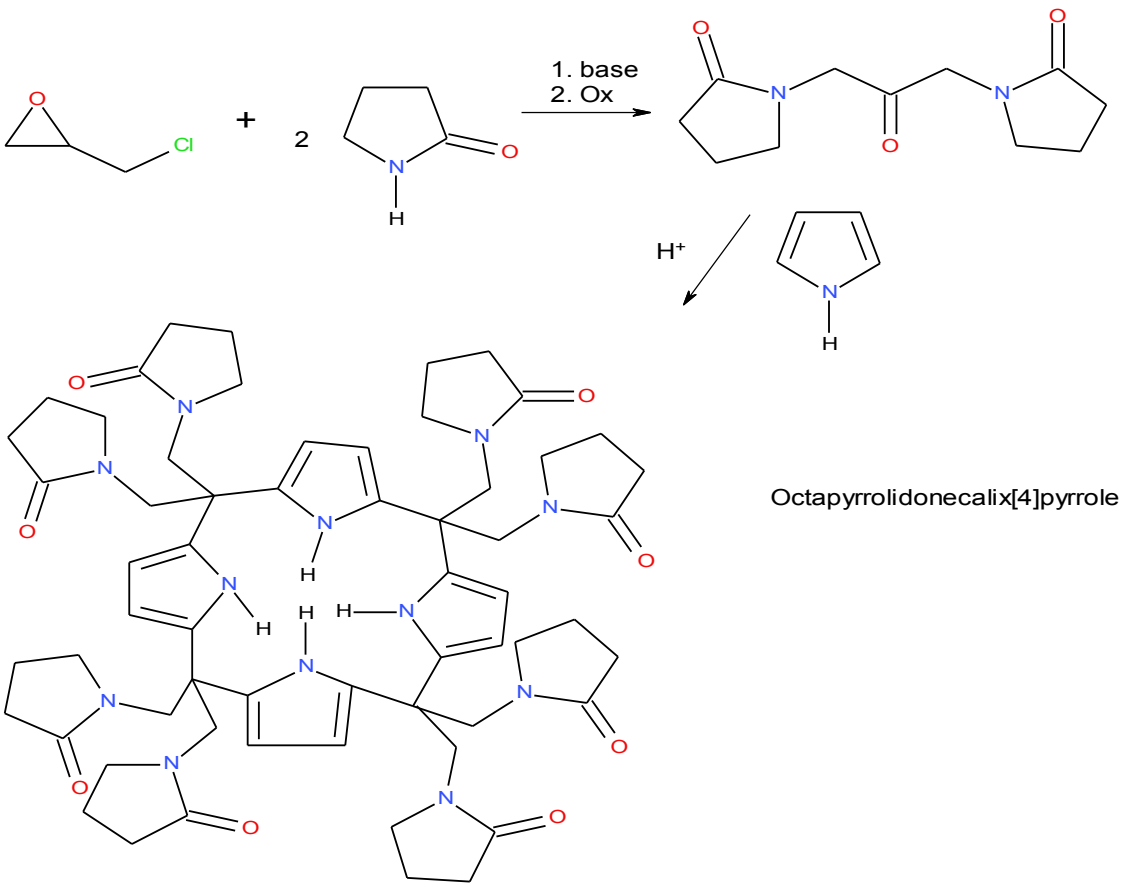
Pyrolporphyrins

The above is an example; however, this basic pyrrolidoneporhyrin would be a good place to start because the starting acetal is readily available. Lengthening the alkyl chain between the aldehyde and pyrrolidone would be a logical extension of this chemistry. Many other possibilities exist for example:



R=aliphatic or aromatic or mixtures substituted with hydrogen, or halogen, oxygen, sulfur or phosphorous or mixtures of said groups

Pyrrolidonecalixpyrrole:



The 1,3 bromide and I believe the chloride derivatives of acetone are commercially available.

With regard to porphyrinic possible structures, they are extensive as this chemistry has generated thousands of references. For example:

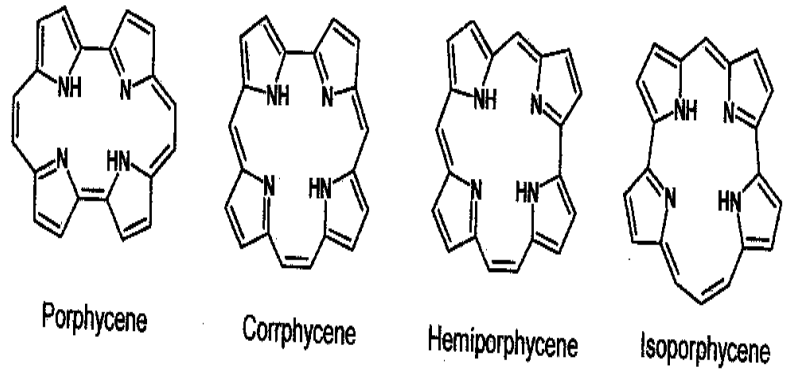


Fig. 7. Porphyrin analogues

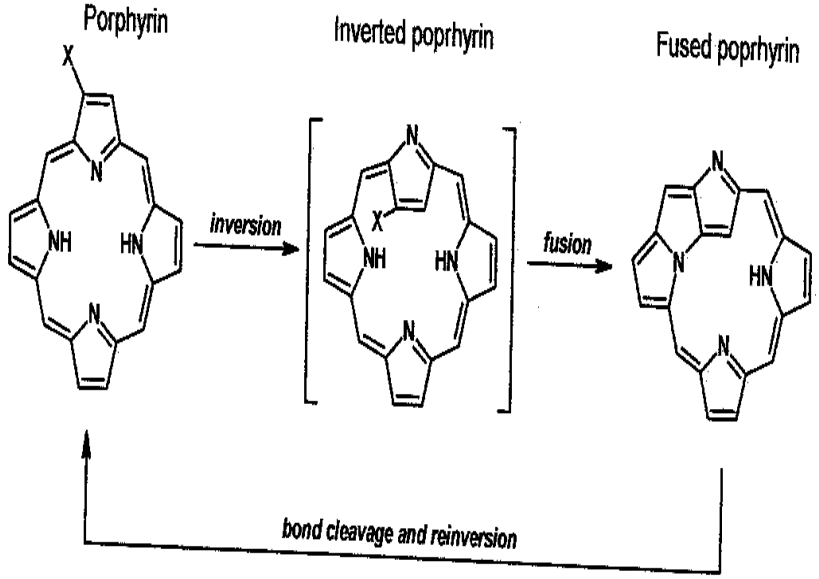


Fig. 8. Inverted and fused porphyrins

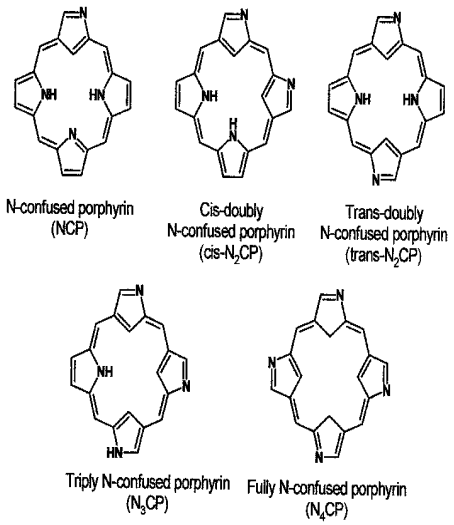


Fig. 9. Confused porphyrins

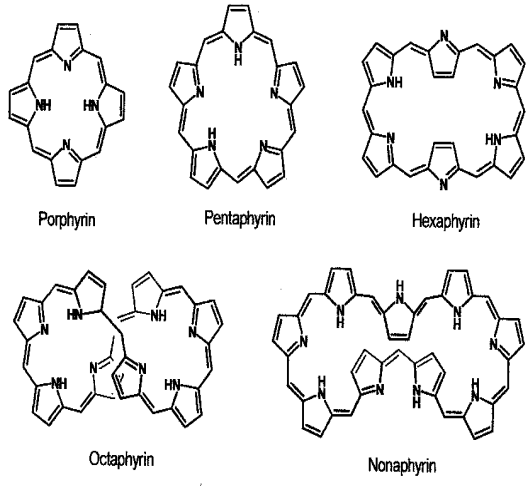
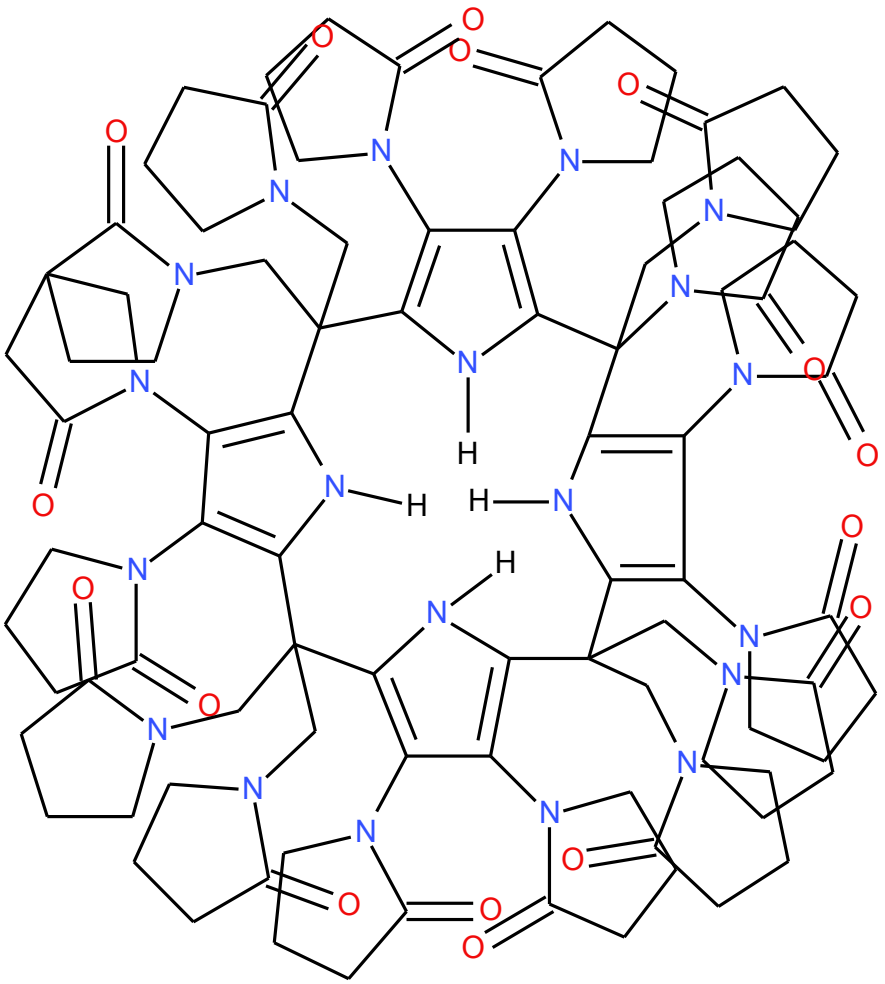


Fig. 10. Expanded porphyrins

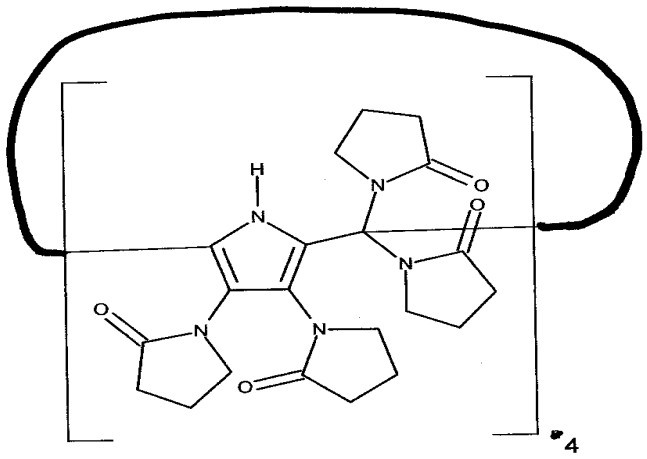
Obviously all of the above variations can have numerous pyrrolidone and other derivatives probably in the thousands. This doesn't even include the calixpyrroles! The point is that making available simple starting materials would be very welcomed. For it would allow workers interested in such modified macrocycles the ability to experiment. Some of the possible end uses such as photo cell ingredients would require significant quantities of said building blocks.



16-pyrrolidonecalix[4]pyrrole

Note the ketones are shown with 2 carbon spacers for clarity.

Although this looks crowded, the meso pyrrolidones are above and below the calixpyrrole ring while the beta pyrrolidone derivatives are in the plane of the ring. Or more simply:



The above structure could have very interesting properties and it is conceivable that it could exist as the condensation chemistry is straight forward and well known.
I could draw many other structures but would rather leave this in the hands of other experimenters.

Cucurbituril like Macrocyclics

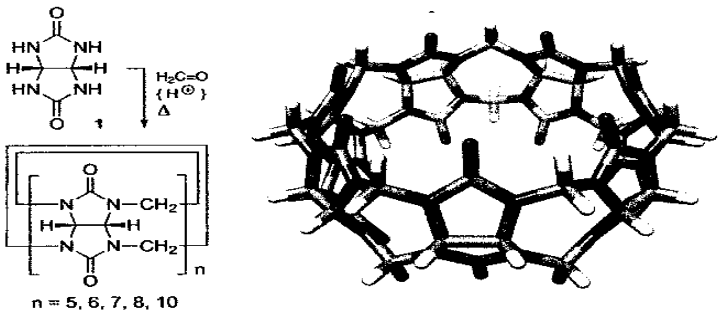
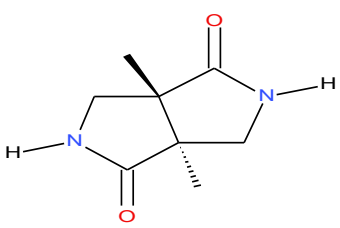
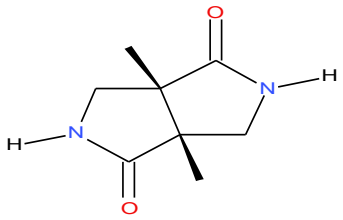
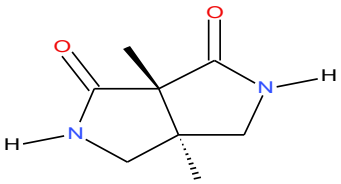
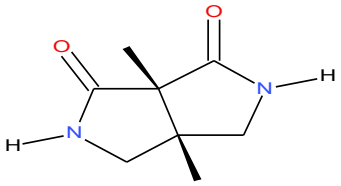
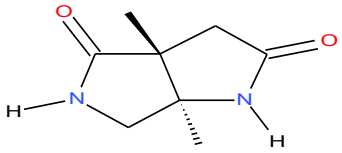
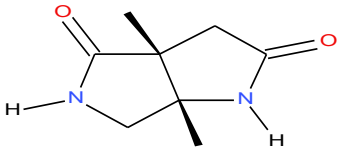
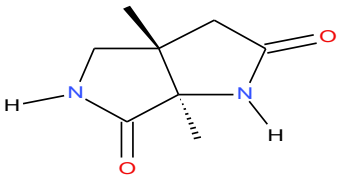
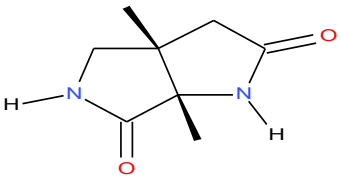
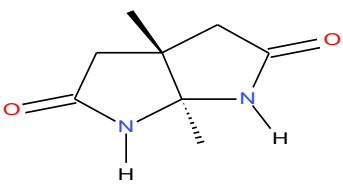
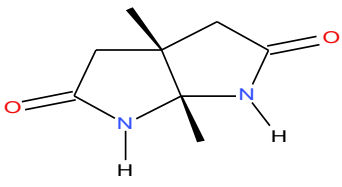


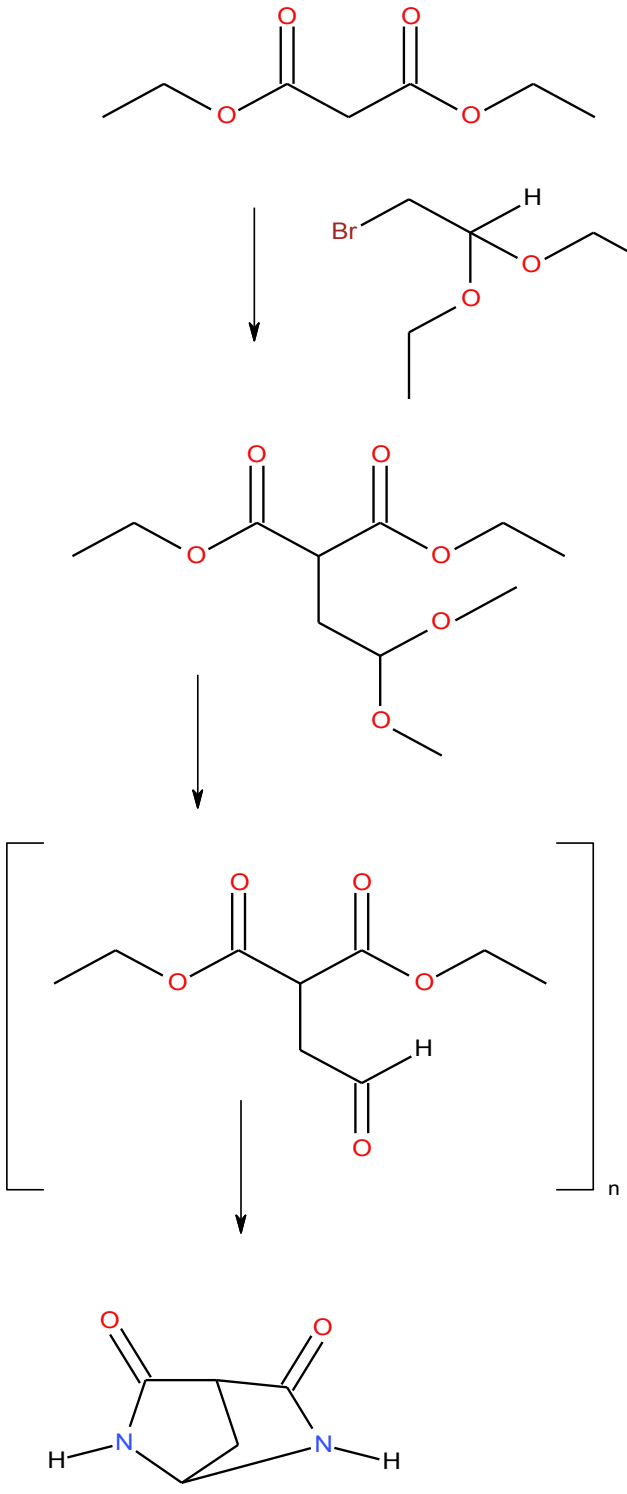
Fig. 1 Preparation of CB[n]s from glycoluril (1) and formaldehyde under acidic conditions. Structure of CB[7] from X-ray diffraction (carbon atoms in grey, hydrogens in white, nitrogens in blue and oxygens in red).

This chemistry dates back to 1905 when Behrend et. al. condensed formaldehyde with glycouril resulting in a white powder in good yield. Not until Mock et. al. during the eighties, discovered the unique structure of this condensate(fig 1) did interest explode. The name comes from the shape of the molecule, like a pumpkin of the cucurbitaceae family.

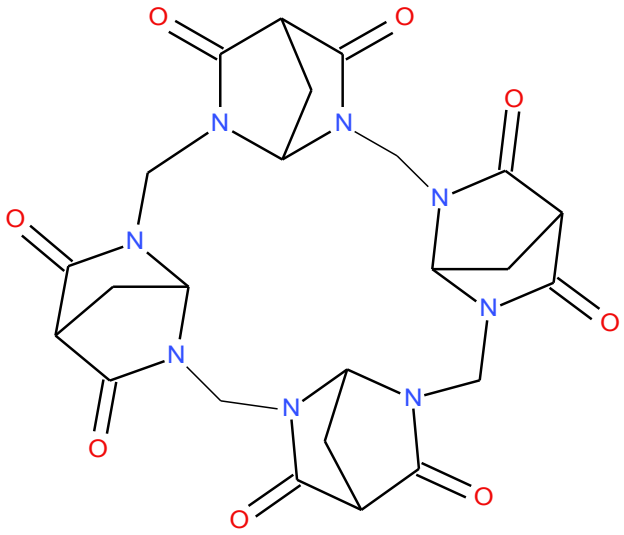
Thinking about using some pyrrolidone type molecule in related structures, that must be difuntional, led to the following structures;

Although each can be synthesized, they have several isomers each and can fit in a ring in several ways. This led to the following norbornane type structure which has no isomers. It can be synthesized as follows;

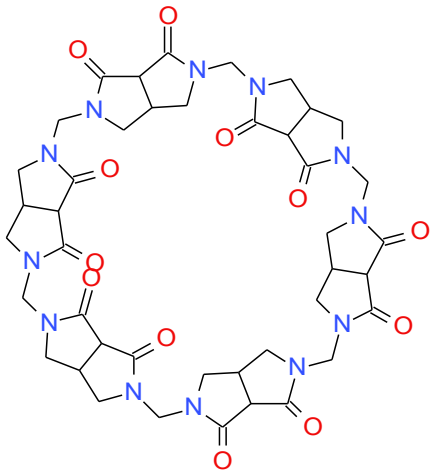


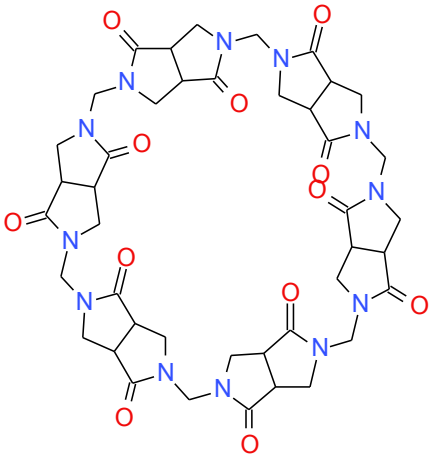
Reaction of the bis-pyrrolidone with formaldehyde catalyzed with acid could result in the following Macrocycle;



This macrocycle would have very interesting properties such as the ability to complex with many types of molecules, delivering drugs to bodily targets, low toxicity and easy excretion et. cetera.

Other examples (shown in simplest form):





As shown above, larger rings could result from the other structures and might be harder to form?

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REVIEW

Cucurbituril chemistry: a tale of supramolecular success

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This review highlights the past six year advances in the blossoming field of cucurbit[n]uril chemistry. Because of their exceptional recognition properties in aqueous medium, these pumpkin-shaped macrocycles have been generating some tremendous interest in the supramolecular community. They have also become key units in various self-organizing and stimulus-controlled assemblies, as well as in advanced materials and drug carriers. The scope of this review is limited to the main family of cucurbit[n]urils (n = 5, 6, 7, 8, 10). The reader will find an overview of their preparation, their physicochemical and biological properties, as well as their recognition abilities towards various organic and inorganic guests. Detailed thermodynamic and kinetic considerations, as well as multiple applications including supramolecular catalysis are also discussed.

Rehrend's experiments and upon complexation with calcium

Rather than paraphrasing I have copied the abstract of this review so that the significant interest in these compounds suggests that new structures would be of real interest.

Commercial Opportunities:

Companies in the business of manufacturing pyrrolidone based specialties such as Ashland and BASF along with numerous smaller entities especially in China, could manufacture a variety of molecules designed to allow the end users to prepare the myriad macrocyclic structures. Just like PVP or NMP, the end users would develop the applications that would result in commercial success. All specialties start out as orphans but the fact that they are commercially available affords the inventor a chance at exclusivity and originality not to be missed! What then can be offered commercially?